

Application No.: 10/076,071

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

Claims 1-530 (Canceled).

531. (New) A method of treating an angiogenic disease or condition in an animal comprising administering to the animal an effective amount of a peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

532. (New) The method of Claim 531 wherein:

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, glutamic acid, lysine, hydroxylysine, histidine, arginine, or α -hydroxymethylserine, and

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Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, glutamine, cysteine, methionine, lysine, hydroxylysine, histidine, arginine, or α -hydroxymethylserine.

533. (New) The method of Claim 531 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine or α -hydroxymethylserine.

534. (New) The method of Claim 531 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

535. (New) The method of Claim 531 wherein Xaa₃ is lysine.

536. (New) The method of Claim 531 wherein:

Xaa₁ is aspartic acid, glutamic acid, arginine, lysine, threonine, serine or α -hydroxymethylserine,

Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and

Xaa₃, when present, is lysine.

537. (New) The method of Claim 536 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine or α -hydroxymethylserine.

538. (New) The method of Claim 537 wherein Xaa₂ is glycine, alanine, valine, leucine or isoleucine.

539. (New) The method of Claim 538 wherein P₁ is Asp Ala His or Asp Ala His Lys.

540. (New) The method of Claim 539 wherein P₁ is Asp Ala His Lys.

541. (New) The method of Claim 536 wherein Xaa₁ is arginine, lysine, threonine, serine or α -hydroxymethylserine, and Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine or α -hydroxymethylserine.

542. (New) The method of Claim 541 wherein P₁ is Thr Leu His, HMS HMS His or Arg Thr His.

543. (New) The method of Claim 531 wherein n is 0-10.

544. (New) The method of Claim 543 wherein n is 0-5.

545. (New) The method of Claim 544 wherein n is 0.

546. (New) The method of Claim 531 wherein P₂ comprises a metal-binding sequence.

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547. (New) The method of Claim 546 wherein P_2 comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,
 (Xaa₄)_m His Xaa₂ Xaa₅,
 (Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or
 (Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

548. (New) The method of Claim 547 wherein Xaa₅ is Orn or Lys.

549. (New) The method of Claim 546 wherein P_2 comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,
 [(Xaa₄)_mXaa₅Xaa₂His]_r,
 [(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or
 [(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

550. (New) The method of Claim 546 wherein P_2 comprises a sequence which binds Cu(I).

551. (New) The method of Claim 550 wherein P_2 comprises one of the following sequences:

Met Xaa₄ Met,
 Met Xaa₄ Xaa₄ Met,
 Cys Cys,
 Cys Xaa₄ Cys,
 Cys Xaa₄ Xaa₄ Cys,
 Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
 Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
 Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
 Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ-Glu Cys Gly.

552. (New) The method of Claim 551 wherein P_2 is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

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553. (New) The method of Claim 531 wherein P_2 comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

554. (New) The method of Claim 553 wherein P_2 is hydrophobic or an arginine oligomer.

555. (New) The method of Claim 531 wherein at least one of the amino acids of P_1 other than β -alanine, when present, is a D-amino acid.

556. (New) The method of Claim 556 wherein Xaa_1 is a D-amino acid, His is a D-amino acid, or both Xaa_1 and His are D-amino acids.

557. (New) The method of Claim 557 wherein all of the amino acids of P_1 other than β -alanine, when present, are D-amino acids.

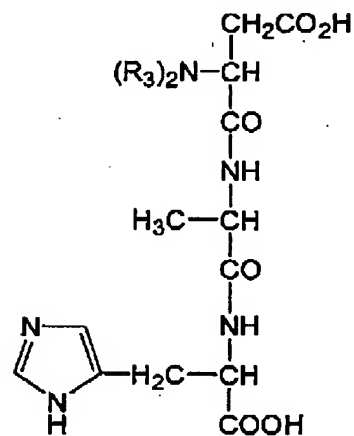
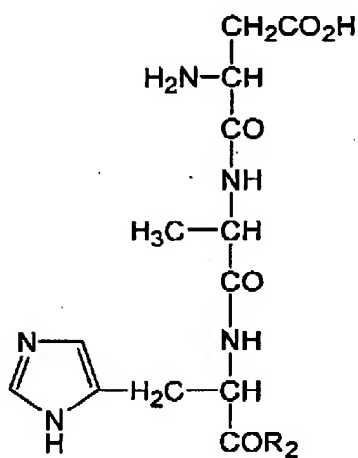
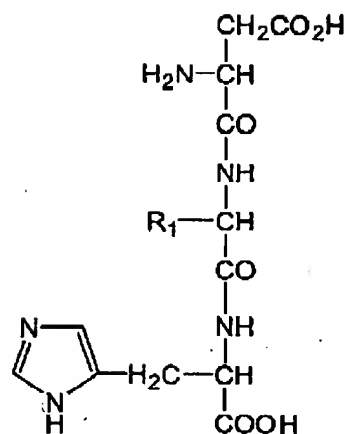
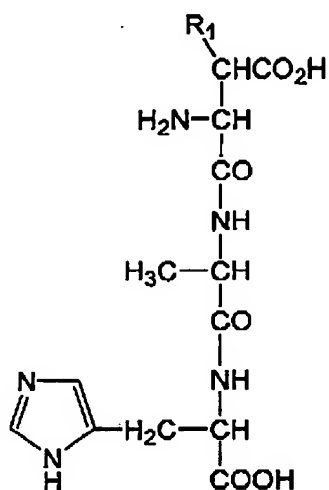
558. (New) The method of Claim 555 wherein at least 50% of the amino acids of P_2 are D-amino acids.

559. (New) The method of Claim 531 wherein at least one amino acid of P_1 , at least one amino acid of P_2 , or at least one amino acid of P_1 and at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

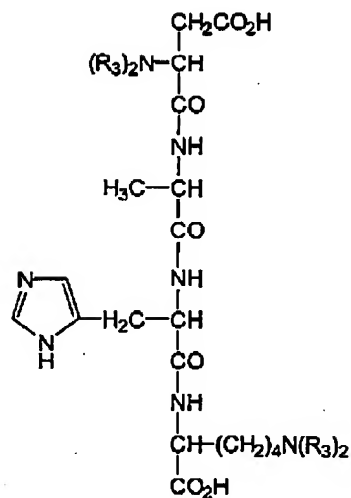
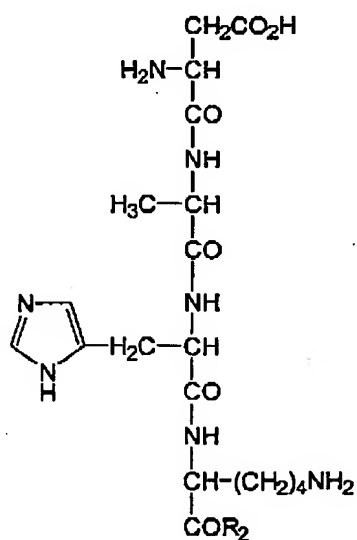
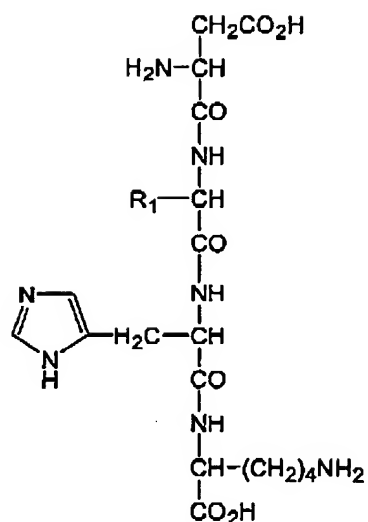
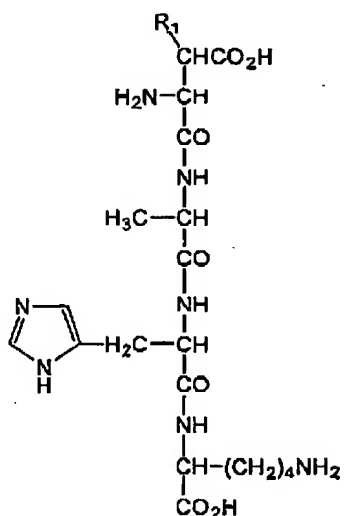
560. (New) The method of Claim 559 wherein the terminal $-\text{COOH}$ of P_1 - P_2 is substituted to produce $-\text{COR}_2$, wherein R_2 is $-\text{NH}_2$, $-\text{NHR}_1$, $-\text{N}(\text{R}_1)_2$, $-\text{OR}_1$, or $-\text{R}_1$, wherein R_1 is an alkyl, aryl or heteroaryl.

561. (New) The method of Claim 559 wherein n is 0 and P_1 has one of the following formulas:

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wherein:

 R_1 is an alkyl, aryl, or heteroaryl; R_2 is $-NH_2$, $-NHR_1$, $-N(R_1)_2$, $-OR_1$, or $-R_1$; and

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R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

562. (New) The method of Claim 561 wherein R_2 is $-NH_2$.

563. (New) The method of Claim 531 wherein the method further comprises administering an effective amount of another metal-binding compound in combination with the peptide.

564. (New) The method of Claim 563 wherein the metal-binding compound binds iron.

565. (New) The method of Claim 564 wherein the iron-binding compound is deferoxamine mesylate.

566. (New) The method of Claim 563 wherein the metal-binding compound binds Cu(I).

567. (New) The method of Claim 566 wherein the Cu(I)-binding compound is a peptide.

568. (New) The method of Claim 567 wherein the Cu(I)-binding peptide comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,

Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],

Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],

Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or

γ -Glu Cys Gly,

wherein Xaa₄ is any amino acid.

569. (New) The method of any one of Claims 531-568 wherein the angiogenic disease or condition is a neoplastic disease, a connective tissue disorder, psoriasis, an ocular angiogenic disease, a cardiovascular disease, a cerebral vascular disease, hemophiliac joints, an immune disorder, a benign tumor, hypertrophy, endometriosis, polyposis, or obesity.

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570. (New) The method of Claim 569 wherein the angiogenic disease or condition is a neoplastic disease.

571. (New) The method of Claim 570 wherein the neoplastic disease is a tumor.

572. (New) The method of Claim 571 wherein the tumor is located in the bladder, brain, breast, kidney, liver, pancreas, lung, cervix, ovary, prostate, stomach, intestines, colon, rectum, or uterus.

573. (New) The method of Claim 570 wherein the neoplastic disease is tumor metastasis.